Treatment Of Chronic Hepatitis B In Patients With Decompensated Cirrhosis

Norah A. Terrault, M.D., M.P.H.
Assistant Professor of Medicine, University of California, San Francisco

Overview of Treatment Goals

Antiviral therapy with a sustained suppression of viral replication is associated with these important benefits in cirrhotic patients with decompensation: (1) clinical stabilization and even reversal of symptoms of decompensation; (2) delayed need for liver transplantation; (3) reduced risk of HBV recurrence following transplantation; and (4) improved survival.

A sustained suppression of HBV replication is critical in achieving and maintaining clinical benefits. Long-term, essentially indefinite, therapy is recommended. As in any population on long-term treatment, the emergence of resistance is a primary concern and, in patients with cirrhosis, the emergence of drug-resistant HBV infection has been associated with worsening of liver decompensation and death in some patients. Treatment algorithms that provide sustained suppression of HBV replication and minimal risk of drug resistance are highly desirable in this patient population.

For those patients with decompensated cirrhosis undergoing liver transplantation, control of HBV replication is also important in insuring long-term graft survival. Recurrent infection in the graft can lead to graft failure or death. The risk of HBV reinfection post-LT is related largely to the level of HBV replication at time of transplantation.[1-3] Thus, for patients with chronic HBV on the waiting list for transplantation, achievement of low levels of HBV DNA and prevention of multi-drug-resistant HBV infection are important dual goals of pre-transplant antiviral therapy.[4]

Current Guidelines for Treatment of Patients with Decompensated Disease

There are four FDA-approved therapies for HBV, alpha interferon (IFN), pegylated interferon alfa-2a (PEG-IFN), lamivudine (LAM), adefovir dipivoxil (ADV), and entecavir (ETV). IFN, however, is not recommended in patients with cirrhosis, as it is associated with dose-limiting cytopenias, a heightened risk of bacterial complications, and, rarely, the precipitation of worsening of liver function. LAM, ADV, and ETV are the agents of choice in patients with cirrhosis including those awaiting liver transplantation. There are several studies using LAM and ADV (alone and in combination) in patients with decompensated cirrhosis, but no clinical studies of ETV in decompensated cirrhotics have been published as yet. There are preliminary data on the safety and efficacy of ETV in compensated cirrhosis.[5]

The published practice guidelines from the AASLD, AGA, and APASL speak to the issue of antiviral therapy in decompensated cirrhosis. These guidelines are consistent in recommending: (1) avoidance of IFN; (2) long-term (indefinite) therapy; and (3) the concurrent consideration of liver transplantation. However, the guidelines are “outdated,” and do not include recently approved antivirals. The potential advantages and disadvantages of the three approved antiviral agents for treatment of chronic HBV in patients with decompensated cirrhosis are detailed in Table 1.

Antiviral Therapy in Patients With Decompensated CIrrhosis

Who Should be Treated?

All patients with decompensated cirrhosis and elevated HBV DNA levels should be started on antiviral therapy as soon as the diagnosis is established, with the dual goals of stabilizing or improving liver function and achieving viral suppression prior to transplantation in those who are transplant candidates. For compensated cirrhotic patients without undetectable HBV DNA

levels who are awaiting transplantation (e.g., with HCC as primary indication), antiviral therapy can be initiated at the time of transplantation.

Studies have shown that clinical improvements tend to lag behind virological responses. Studies of LAM and ADV in patients with decompensated disease found a median clinical response time of ~6 months.[6-8] Thus, patients with severely decompensated liver disease may die before the clinical benefits of antiviral treatment can be realized, emphasizing the importance of concurrent consideration of liver transplantation.

How Should Patients on Treatment Be Monitored?
Once treatment is initiated, monitoring for virological response to therapy (achievement of undetectable HBV DNA levels) is important if clinical benefits are to be realized. Additionally, duration of therapy and failure to achieve suppression of HBV DNA early in treatment (within the first 6 months, generally) are risk factors for nucleos(t)ide resistance.[9,10] Failure to achieve HBV DNA suppression with one drug should prompt consideration of additional or alternative drugs. The rate of HBV DNA decline is also of importance in those awaiting transplantation, as an undetectable HBV DNA level is desirable pre-LT. The reported median log decline in HBV DNA levels after 24 weeks of treatment in compensated chronic HBV disease is greater with ETV than with LAM and ADV.

Regular monitoring for drug resistance during prolonged treatment is essential in cirrhotic patients. Hepatic “flares” (increased ALT levels to >5-10 ULN) occur during the first year of antiviral therapy in 5-10% of patients. Flares occurring with a declining HBV DNA level reflect enhanced immune activation related to effective antiviral therapy, whereas those occurring with a rising HBV DNA level reflect the development of drug resistance. The emergence of drug-resistant HBV is associated with an increased frequency of hepatitis flares, clinical deterioration, worsening of liver decompensation, and even liver-related death. Thus, monitoring of HBV DNA levels at regular intervals should be used to detect virological breakthrough early and prior to worsening of clinical status.

All of the oral agents have an excellent safety record in patients with compensated liver disease. Additionally, LAM and ADV has established safety and tolerability in patients with decompensated cirrhosis and those awaiting liver transplantation. Dose adjustments are required with use of LAM, ADV, and ETV in patients with renal dysfunction. Due to concerns regarding potential renal toxicity related to higher dose ADV therapy, monitoring of renal function is recommended in those on long-term ADV therapy.

Selection of Antiviral Therapy
As highlighted, IFN is contraindicated. Three FDA-approved oral agents are available (LAM, ADV, ETV), and several other antiviral agents with HBV activity are approved for HIV (emtricitabine, tenofovir) or are in advanced phases of study (clevudine, telbuvidine). Data on the safety and efficacy of these unapproved HBV drugs in patients with decompensated cirrhosis are lacking.

Treatment needs to be individualized. A primary determinant of antiviral(s) choice is the presence of drug-resistant HBV (active or archived). Treatment options are generally more limited for patients with preexisting drug resistance. Additional factors of relevance in the choice of antiviral agent are (i) HBV DNA level, (ii) severity of liver disease, and (iii) expected time to transplantation.

For patients with decompensated cirrhosis who are nucleos(t)ide-naïve, LAM, ADV, or ETV are possible options. Sustained suppression of HBV replication with LAM is associated with improved indices of liver synthetic function and clinical status.[6,7,11] While LAM has a long safety record in patients with decompensated cirrhosis and low cost, the high risk of viral resistance with prolonged therapy is a major limitation. Thus, for treatment-naïve patients, ADV or ETV are the drugs of choice. LAM monotherapy should only be considered in select patients – namely those with low or undetectable HBV DNA levels for whom the time to LT is expected to be less than 6 months. For patients on ETV or ADV with suboptimal virologic response after 3-6 months of therapy, additional or alternative drugs should be used.

Patients with decompensated cirrhosis and LAM-resistant HBV infection are more challenging. ADV therapy is the best studied. In decompensated cirrhotics with LAM-resistance, treatment with ADV resulted in improvement in liver enzymes, indices of liver synthetic function, and clinical stabilization.[8,12] The risk of ADV resistance in these patients appears higher if ADV replaced LAM rather than added on (combination therapy), and greater in those with a suboptimal virological response to ADV.[10] For patients with ADV resistance or both LAM and ADV resistance, data suggest ETV and tenofovir are options.[10,13] ETV, like ADV, is approved for treatment of lamivudine-resistant HBV, but virological and clinical responses in patients with decompensated cirrhosis are not available at yet. Genotypic ETV resistance has been reported in 7% of LAM-refractory patients after 1 year of treatment.[14] Tenofovir is an approved agent for HIV, which also has activity against wild-type and LAM-resistant HBV; case reports of TVF treatment in patients showing a suboptimal virological response to ADV have been published, though the total number of treated patients is small. Taken together, the best options for patients with decompensated cirrhosis with LAM-resistant HBV infection appears to be combined ADV plus LAM. Other drug combinations that have not been studied but would be predicted to be effective are LAM plus tenofovir, or ETV plus ADV.

Table 1
Treatment Options for Chronic HBV in Decompensated Cirrhosis, Including Those Awaiting Liver Transplantation

Drug	Effective Against	Advantages	Disadvantages
LAM	Wild-type ADV-R HBV HBIG-associated S gene mutants	Low cost Well-tolerated; no renal toxicity Established safety and efficacy in decompensated cirrhosis and LT patients	Resistance risk 20% after 1 year, 50% after 3 years Cross-resistance with other L nucleosides
ADV	Wild-type LAM-R HBV ETV-R HBV	Low rate of resistance (2% at 2 years) Well-tolerated Established safety and efficacy in cirrhotic and LT recipients	Higher costs (c/w LAM) Rate of resistance approaches 20% after 4 years mono-therapy; higher in LAM-R treated with ADV alone Possible renal toxicity
ETV	Wild-type LAM-R HBV ADV-R HBV	Low rate of resistance (0% at 2 years if wild-type HBV) Potent antiviral activity; decline in	Higher cost than LAM or ADV Preexisting LAM-R increases risk of ETV-R

		HBV DNA more rapid and frequent than LAM Renal toxicity not an issue	No safety and efficacy data in decompensated cirrhosis and LT recipients

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